Apremilast (OTEZLA) Tablets in Psoriasis and Psoriatic Arthritis
Criteria for Use
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. Local adjudication should be used until updated guidance and/or CFU are developed by the National PBM. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. ***THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.***

The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria *(If the answer to ANY item below is met, then the patient should NOT receive apremilast.)*

- ☐ Hypersensitivity to apremilast or any formulation excipients
- ☐ Concomitant therapy with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin), which may cause loss of efficacy of apremilast
- ☐ Untreated or unstable depression or suicidality. (For patients with a history of depression or suicidality, see **Depression** under **Issues for Consideration.**)
- ☐ Concurrent treatment with biologic therapy (safety has not been studied)
- ☐ Structural joint damage from PsA (Evidence supports the use of TNFIs or ustekinumab rather than apremilast. See *Potential Limitations of Apremilast*.)

Inclusion Criteria

☐ Adult (18 years of age or older) with (**A** and / or **B**):

__**A.** Diagnosis of plaque psoriasis for 6 or more months (chronic plaque psoriasis, CPP) that is moderate to severe and patient is a candidate for systemic therapy (antipsoriatic or ultraviolet).

__**B.** Active, predominantly peripheral, nonerosive psoriatic arthritis (PsA) with diagnosis for 6 or more months and involving at least 3 swollen and 3 tender joints

☐ **C. AND** Received/-ing VA care or consultation from a dermatologist (for CPP), or a rheumatologist (for PsA without psoriasis), or both dermatologist and rheumatologist (for PsA with psoriasis) or other experts in psoriatic and/or rheumatologic diseases.

☐ **D. AND** Inadequate control or loss of response despite an adequate trial of **methotrexate, leflunomide or sulfasalazine** (UNLESS the patient has a contraindication, risk factor for serious adverse effect, intolerance, hardship with required therapeutic monitoring (e.g., long distance to clinic, difficulties with transportation) or refuses methotrexate injections if applicable). *For adequate trial durations, refer to gray information box below*.

☐ **AND EITHER E1 OR E2**

__**E1.** Contraindication to, risk factor for serious adverse effect (e.g., recurrent infections, heart failure, personal history of demyelinating disease, history of malignancy, travel to regions with high risk of tuberculosis), hardship with required therapeutic monitoring (e.g., long distance to clinic, difficulties with transportation) or refuses injections of tumor necrosis factor inhibitors (TNFIs)

__**E2**. Intolerance or inadequate response to **two TNFIs** (i.e., adalimumab, etanercept, or infliximab for PsA or CPP; and certolizumab or golimumab for PsA). A past trial of the non-TNFI biologic ustekinumab may count in lieu of one TNFI trial and ustekinumab may be tried before apremilast but ustekinumab should not be required prior to apremilast. *For adequate trial durations, refer to gray information box below*. *Also refer to the Criteria for Use of Biologics in Psoriasis and Psoriatic Arthritis available at www.pbm.va.gov or http://vaww.pbm.va.gov* .

- Refer to *Methotrexate Contraindications and Risk Factors for Serious Adverse Effects* under *Issues for Consideration.*
- If accessible, PUVA or UVB may be used (only for CPP) instead of one of the oral small molecule immunomodulators.
- Alternative small molecule immunomodulators include methotrexate, sulfasalazine and leflunomide for CPP or PsA. Past trials of acitretin, cyclosporine, azathioprine, hydroxyurea, and 6- thioguanine for CPP and past trials of cyclosporine, hydroxychloroquine, azathioprine, gold and penicillamine for PsA may also count but should not be required prior to apremilast.
- If tolerated, **adequate trial durations** are as follows:
  - For methotrexate: NO or minimal response after 3 months at doses of 15–25 mg/wk and inadequate partial response to treatment after 6 months at doses of 15–25 mg/wk (or lower doses if limited by toxicity).
  - For other immunomodulators: NO or minimal response after 3 months at recommended doses (or lower if limited by toxicity); inadequate partial response to treatment after 6 months.
  - For biologic agent: NO or minimal response after 3 months or inadequate partial response after 6 months.
  - For PUVA and UVB: NO or minimal response after 12 treatments; inadequate partial response after 24 treatments.

Dosage and Administration

Refer to Product Information.

Dosage Titration: A gradual 5-day initial titration is suggested to improve tolerability. The dose should be started in the morning of Day 1 at 10 mg twice daily for 4 doses, then increased to 20 mg twice daily for 4 doses, then 30 mg twice daily thereafter. Starter packs are available.

Dosage in Severe Renal Impairment (eCrCl less than 30 ml/min): Reduce daily doses by one half. For initial dosage titration, give only the morning doses of the Starter Pack. The maintenance dose should be reduced to 30 mg once daily.

Dosage in Hepatic Impairment: No dosage adjustment is necessary in moderate (Child-Pugh B) and severe (Child-Pugh) hepatic impairment.

Discontinuation: Discontinue apremilast if there is NO or only minimal benefit by 16 weeks (i.e., primary treatment failure) or if patient develops signs of disease progression or joint erosion during therapy. There is a lack of evidence that apremilast prevents disease progression or joint erosion. Patient should be switched to alternative biologic therapy.

Monitoring

- Emergence or worsening of depression, suicidal thoughts or other mood changes.
- Weight decrease.
- Regular re-assessments for continued benefit and potential risks of apremilast therapy, particularly beyond 1 year

Issues for Consideration

FDA-approved Indications:

- Treatment of adult patients with **active psoriatic arthritis**.
- Treatment of patients with **moderate to severe plaque psoriasis** who are candidates for phototherapy or systemic therapy.

Severity of Plaque Psoriasis

- Moderate to severe psoriasis may be described as psoriasis in which one cannot achieve or would not be expected to achieve adequate control using topical agents, with adequacy defined by the patient's own perception of the disease and its burdens.
- Severe psoriasis may be described as disease that is disabling or impairs the patient's quality of life (self-reported), including ability to work and activities of daily living AND the disease does not have a satisfactory response to treatments that have minimal risks, the patient is willing to accept life-altering adverse effects to achieve less disease or no disease, AND generally more than 10% of body surface area is involved with disease. Psoriasis may also be considered severe when other factors apply such as the patient's attitude about the disease; location of disease (e.g., face, hands, fingernails, feet, genitals); symptoms (e.g., pain, tightness, bleeding, or severe itching); arthralgias or arthritis.

Potential Limitations of Apremilast

- In psoriatic arthritis, apremilast was associated with 67% to 100% reduction in enthesitis and dactylitis counts only after 52 weeks of therapy in a study without a placebo control.[1] There were no significant benefits for enthesitis and dactylitis counts at 16 weeks in placebo-controlled trials. There is a lack of evidence for beneficial effects for uveitis.
- The efficacy of apremilast for axial disease is unclear at this time. TNFIs or ustekinumab would be preferred for axial disease.
- Exploratory analyses suggest that apremilast may not be efficacious in TNFI failures.
- Radiographic response has not been evaluated; apremilast has not been shown to have a disease-modifying effect. TNFIs or ustekinumab would be preferred when disease modifying effects are indicated.
- Long-term studies and experience beyond 1 year are lacking.

Concurrent Antipsoriatic Therapies

- There was no additional benefit or risk when apremilast was used concomitantly with methotrexate. Apremilast was also used concomitantly with sulfasalazine, leflunomide, corticosteroids and NSAIDs in clinical trials that showed safety and efficacy.

Lack of Serious Infections, Immunosuppression, Bone Marrow / Hematologic Suppression and Organ Damage

- Upper respiratory tract infections, none serious, occurred during 16 weeks of apremilast study treatment in about 9% of patients with CPP and 4% of patients with PsA. No serious or systemic bacterial or opportunistic infections and no immunosuppressive adverse events were reported in trials up to 52 weeks in duration.
- There was no evidence of mucosal, pulmonary, hepatic or renal injury during apremilast clinical trials. ALT and AST abnormalities (3-fold increases over the upper limit of normal) were observed in numerically more apremilast patients than placebo patients in clinical trials; however, there were no cases that met criteria for liver injury, and the prescribing information makes no recommendations for monitoring liver transaminases.

Depression

- Depression was reported in 1.3% of apremilast patients with CPP and 1.0% of patients with PsA (versus 0.4% and 0.8% of placebo patients, respectively) in 16-week clinical trials. Careful FDA review of the clinical trial data determined that there was no evidence of an increased risk of suicide with apremilast therapy.
- Carefully weigh risks versus benefits in patients with a history of depression and/or suicidal thoughts or behavior or in patients who develop these symptoms during therapy. Family members and caregivers should be instructed to be alert for development or worsening of depression or suicidality in patients.

Weight Decrease

- Weight decreases of 5% to 10% of body weight were observed in 12% of patients with CPP and 10% of patients with PsA (compared with 5% and 3.3% of patients on placebo, respectively) in 16-week clinical trials. Monitor weight regularly and consider discontinuation of apremilast if unexplained or excessive weight loss occurs.

Drug Interactions

- Concomitant therapy with **strong CYP450 enzyme inducers** (e.g., **rifampin**, phenobarbital, **carbamazepine**, and **phenytoin**) is not recommended because these agents may lead to reduction in systemic exposure of apremilast and loss of its efficacy.
- Carefully weigh potential risks versus benefits before using apremilast in patients taking **other phosphodiesterase-4 inhibitors.** This precaution is in addition to the prescribing information for apremilast and is based on pharmacologic similarities with **roflumilast** (a selective PDE4 inhibitor used for COPD). Roflumilast has also been associated with decreases in weight and an increased risk of psychiatric events including depression and suicidality.

Methotrexate Contraindications and Risk Factors for Serious Adverse Effects

A Trial of Methotrexate Should Not Be Required Before Biologics in the Presence of Any of the Following Conditions:

Contraindications:

- Renal insufficiency (CrCl ≤ 60 ml/min)†
- Persistently abnormal liver function or enzyme tests and, if available, other markers of hepatic damage such as procollagen type III n-terminal peptide (PIIINP) levels
- Liver disease, including active or recurrent hepatitis and hepatic fibrosis or cirrhosis on liver biopsy (biologics may also not be advisable in this situation)
- Active infectious disease, including active untreated tuberculosis or advanced HIV infection; excludes acute infections for which methotrexate may be temporarily withheld
- Immunodeficiency (does not apply to treatment with other immunosuppressives such as biologic agents)
- Blood dyscrasias or cytopenias (contraindication for methotrexate; requires caution and risk-benefit evaluation for biologics)
- Conception in men or women; patients planning conception or patients of childbearing potential and not using adequate contraceptive method (conception should be avoided during methotrexate therapy and for at least 3 months after stopping therapy in males or at least one ovulatory cycle in females)
- Pregnant or nursing women
- Pneumonitis or significant pulmonary disease that may interfere with diagnosis or monitoring for methotrexate-induced lung disease / pulmonary fibrosis
- Recent vaccination, especially with live vaccine (also refer to live vaccine and BCG vaccination restrictions for biologics)
- Third-compartment spacing, such as persistent pleural effusion and ascites
- Malignant lymphoma (biologic therapy is also not advisable in this situation)
- Hypersensitivity

Relative Risk Factors (Methotrexate May Be Used, But Not Required)

- Lifetime cumulative dose of methotrexate is 3 grams or greater. Consider alternative systemic therapies at these cumulative doses, given the limitations of existing data to support or refute lifetime dose of methotrexate as a risk factor.
- Significant lifetime alcohol consumption (e.g., past or current use of >1–2 drinks per day). Methotrexate toxicity is associated with a history of total lifetime alcohol intake before methotrexate therapy. The exact amount of alcohol that confers risk is unknown and differs among persons.
- Chronic hepatitis C without evidence of significant liver disease (contraindicated in patients with HCV and cirrhosis).
- Family history of inheritable liver disease
- Obesity (body mass index greater than 30)
- Diabetes mellitus
- History of significant exposure to hepatotoxic drugs (e.g., azathioprine, retinoids, sulfasalazine) or chemicals
- Hyperlipidemia
- Lack of folate supplementation (i.e., folic acid 1 or 5 mg daily or folinic acid 5 mg every 12 h for 3 doses then once every week, with the first dose given 12 hours after the methotrexate dose)

†References: Methotrexate Product Monograph, Pfizer Canada, last updated April 21st, 2011. Available at: http://www.pfizer.ca/en/our_products/products/monograph/280 (No CrCl cutoff is recommended in U.S. product information for methotrexate.) Kalb, et al. Methotrexate and Psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009;60:824–37. Methotrexate Tablets, USP product information (online). DAVA Pharmaceuticals, Inc. Rev. 4/09.

Renewal Criteria

- Documented to have at least partial benefit after 24 weeks of treatment. While 24 weeks can be considered an adequate trial duration for apremilast, some patients may experience further improvement beyond 24 weeks. Consider switching to alternative therapies if there is unsatisfactory response after 24 weeks of treatment.

Prepared: May 2015. Contact: Francine Goodman, National PBM Clinical Pharmacy Program Manager – Formulary, VA Pharmacy Benefits Management Services (10P4P)

[1] Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, Hochfeld M, Teng LL, Schett G, Lespessailles E, Hall S. Longterm (52-week) Results of a Phase III Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis. J Rheumatol. 2015 Jan 15 pii: jrheum.140647. [Epub ahead of print] PubMed PMID: 25593233